The "Bottom-Up" Approach to Estimating Low Dose Risk Cannot Be Considered Conservative

Starr and Swenberg (2013) proposed a "bottom-up" modelling approach, the purpose of which is to bound low-dose cancer risks from chemicals that are found endogenously within the body and thus provide a "reality check" on risk estimates derived by traditional approaches used by Agencies such as the EPA. The approach does not use tumor incidence data from laboratory animals or humans for quantification, but relies only on the endogenous concentration level, C_0, of an internal metric (e.g., N^2-hydroxymethyl-dG mono-adducts in the case of formaldehyde) and the background risk, P_0, for the cancer type of interest. The ratio P_0/C_0 is used to estimate the average slope of the dose-response relationship between risk and the internal dose at low (exogenous) exposures, and an upper bound on this ratio is claimed to be an "upper bound" on the low (exogenous) dose-response slope by virtue of the following procedures inherent in the approach: 1) for purposes of "bounding", all of the background risk is assumed to be due to the endogenous internal dose (as measured, for example, by the endogenous adduct concentration), 2) the dose-response relationship for risk as a function of endogenous adduct concentration is assumed to be linear, and 3) a lower confidence limit, C_{0L}, on the estimate of the endogenous concentration, C_0, is used .

The purpose of this letter is to articulate why the proposed "bottom-up" approach should not be considered to "bound" the range of plausible estimates derived by more traditional approaches. First, the approach is highly reliant on several assumptions such as the appropriate internal moiety and site of initial action have been identified, estimates of internal dose are reasonably accurate, and the range of human variability in factors affecting pharmacokinetics or pharmacodynamics have been suitably considered. These assumptions relating risks to measured adduct levels could be wrong -- leading to a false bound. However, even *if* the relative adduct levels provide an appropriate dose metric for risks, P_0/C_{0L} is not necessarily an upper bound. We focus here on the latter issue which we believe is a fundamental flaw in this approach.

Figure 1 depicts the "bottom-up" approach graphically. The Figure shows that if C_0 was accurately known, the approach could underestimate the dose-response slope at C_0 if the dose-response curve is concave upwards in the vicinity of C_0. The dotted line with slope P_0/C_0 is the linear approximation used in the bottom-up approach to represent the average risk at zero exogenous exposures. The solid black curve in Figure 1 represents a possible dose-response relationship (which, of course, is unobservable near and below C_0). It is clear from this figure that whenever the true dose-response relationship is upward curving in the neighborhood of C_0, the linear assumption used in the "bottom-up" approach is not conservative. Likewise, the upper bound on P_0/C_0 obtained by the use of the lower bound on C_0 is not necessarily an upper bound on the low-dose slope of the true dose-response relationship. The authors of the "bottom-up approach" have not provided any basis to conclude that taking the lower confidence limit on C_0 will necessarily overcome any underestimation by the "bottom-up" approach of the slope at C_0.

Starr and Swenberg (2013) did not contend that the endogenous dose-response relationship was not upward curving, but instead they assume tacitly that a linear dose-response relationship over the endogenous range bounded the slope of all possible endogenous dose-response relationships. This is

incorrect. When a dose-response relationship is curved upwards, a line drawn from a point on the curve to the origin will overestimate the risk within that interval but will underestimate the risk for doses above that point on the curve. A sublinear dose-response relationship over the endogenous range is clearly plausible on biological grounds. For example, it is likely that baseline levels of DNA repair enzymes and other protective systems evolved to deal with endogenous DNA damage would work most effectively for lower levels of endogenous adducts.

The authors note that their approach is consistent with the concept of additivity to background disease processes (Crump et al. 1976) and that the upper bound on P_0/C_0 is directly comparable to the estimate derived from the linearized multistage model. It is useful to indicate that adherence to this concept of additivity does not require the globally linear constraint (i.e. linear all the way down to an origin at zero endogenous dose) imposed by the bottom-up approach but instead only requires local linearity in the proximity of zero exogenous dose.

Figure 1: Graphical Representation of the "Bottom-Up" Approach in a Case in Which the True Dose Response Curves Upward In the (Unobservable) Endogenous Range